Eliglustat (CERDELGA™)

National Drug Monograph (Abbreviated)

March 2015

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

FDA Approval Information[1-3]

Description/Mechanism of Action	Eliglustat is a glucosylceramide analogue, and strong inhibitor of glucosylceramide synthase, decreasing the accumulation of glucosylceramide. Eliglustat is a substrate reduction therapy (SRT) for the treatment of Gaucher disease type 1. In Gaucher disease type 1, there is a deficiency in the enzyme glucocerebrosidase, leading to an accumulation of glucosylceramide (also known as glucocerebroside) in the lysosome of macrophages, resulting in foam cells (also referred to as Gaucher cells). In Gaucher disease type 1, accumulation of Gaucher cells occurs in the liver, spleen, bone marrow, as well as other organs including the lungs, resulting in hepatosplenomegaly, anemia, thrombocytopenia, pulmonary disease, and bone abnormalities including fractures and arthritis.
Indication(s) Under Review in this document	Eliglustat is indicated for the long-term treatment of adult patients with Gaucher disease type 1 who are CYP2D6 extensive metabolizers (EMs), intermediate metabolizers (IMs), or poor metabolizers (PMs) as detected by an FDA-cleared test.
Dosage Form(s) Under Review	Eliglustat is available as 84 mg hard gelatin capsules.
REMS	☐ REMS ☒ No REMS ☒ Postmarketing Requirements
Pregnancy Rating	Eliglustat is Pregnancy Category C.

Executive Summary

Efficacy[1-4]	• Results are available from two Phase III clinical trials with eliglustat in patients with Gaucher disease type 1, ENGAGE in treatment-naïve patients and ENCORE in treatment-experienced patients. • In ENGAGE, patients treated with eliglustat were found to have an improvement in the primary endpoint of reduction in spleen volume at 9 months compared to placebo. • Results of ENCORE reported eliglustat to be non-inferior to imiglucerase in the composite primary endpoint of stability in spleen volume, liver volume, hemoglobin (Hgb) level, and platelet count at 12 months compared to baseline.
Safety[1-4]	• Serious adverse events with eliglustat include ECG changes and potential for cardiac arrhythmias; eliglustat is not recommended in patients with pre-existing cardiac disease, long QT syndrome, and concomitant use of Class 1A and Class III antiarrhythmics. • Eliglustat is a CYP2D6 and CYP3A substrate and is metabolized primarily by the CYP2D6 isoenzyme. Concomitant use of eliglustat with medications that inhibit CYP2D6 and CYP3A may significantly increase eliglustat exposure with subsequent prolongation of the PR, QTc and/or QRS cardiac interval, with potential increased risk for arrhythmias. • Eliglustat is contraindicated in patients who are CYP2D6 EM or IM that are taking a strong or moderate CYP2D6 inhibitor with a strong or moderate CYP3A inhibitor, and in patients who are CYP2D6 IM or PM that are taking a strong CYP3A inhibitor. • Refer to the Safety section of this monograph or the product package insert for

	additional recommendations and considerations for potential drug interactions.
Other Considerations[1]	• Recommendations for dosing eliglustat depend on the results of an FDA-cleared test for determining CYP2D6 genotype and whether the patients are EMs, IMs or PMs.
Potential Impact[1-14]	• Projected place in therapy: Enzyme replacement therapy (ERT) has been the standard of care for Gaucher disease type 1 and is effective for improving the associated hematologic and visceral abnormalities, and bone disease. Three ERTs are available for the treatment of Gaucher disease type 1, and are administered by intravenous (IV) infusion: imiglucerase, taliglucerase alfa, and velaglucerase alfa. Miglustat, an oral SRT, is recommended in patients with Gaucher type 1 where ERT is not an option (miglustat was not as effective as an ERT in a comparison trial and has significant side effects). The optimal place in therapy of eliglustat, also an oral SRT, in Gaucher disease type 1 has not been established. Eliglustat was effective compared to placebo in treatment naïve patients, and non-inferior to the ERT imiglucerase in treatment-experienced patients; however, the long-term outcome benefit and treatment effect on associated bone disease has yet to be established. • Treatment considerations should take into account the risk vs. benefit of available therapies, including patient considerations such as treatment response, safety concerns, adverse effects and tolerability, route of administration, as well as the cost of and access to therapy. Due to the potential for drug interactions, and other safety and efficacy considerations based on the patient's CYP2D6 metabolizer status, patients should have genetic testing by an FDA-cleared test to determine whether they are CYP2D6 extensive metabolizers, intermediate metabolizers, or poor metabolizers for appropriate dosing and to allow for considerations for potential drug interactions.

Background

Purpose for review

Recent FDA approval.
Issues to be determined:
✔ Does the evidence show that eliglustat is safe and effective in the treatment of Gaucher disease type 1?
✔ Does eliglustat offer advantages over current non-formulary treatments for Gaucher disease type 1?
✔ What additional safety issues need to be considered with the use of eliglustat?
✔ Does eliglustat have specific characteristics best managed by the non-formulary process or criteria for use?

Other therapeutic options[5-8]

In addition to eliglustat, miglustat is an SRT used for Gaucher disease type 1. Imiglucerase, taliglucerase alfa, and velaglucerase alfa are ERTs for treatment of this disease.

Non-Formulary Alternatives	Indication	Route of Administration	Dosing Frequency
Miglustat (SRT)	Gaucher disease type 1 where ERT is not an option	Oral	Three times daily*
Imiglucerase (ERT)	Gaucher disease type 1	IV infusion over 1-2 hours	Three times/week to every 2 weeks
Taliglucerase alfa (ERT)	Gaucher disease type 1	IV infusion over 1-2 hours	Every other week
Velaglucerase alfa (ERT)	Gaucher disease type 1	IV infusion over 1 hour	Every other week

*Recommendations for reduced dosing frequency based on side effects or renal impairment

Efficacy (FDA Approved Indications)

Literature Search Summary

A literature search was performed on PubMed/Medline (1976 to February 2015) using the search term eliglustat. The search was limited to studies performed in humans and published in the English language. Reference lists of review articles were searched for relevant clinical trials. The efficacy data provided in this section is based on data from one published Phase 3 clinical trial,[3] as well as information provided in the manufacturer's product information,[1] the FDA medical review,[4] and one review article.[2]

Review of Efficacy[1-4]

- Results from two Phase 3 clinical trials, ENGAGE in treatment-naïve patients and ENCORE in treatment-experienced patients, with eliglustat in patients with Gaucher disease type 1 have been reported.
- In ENGAGE, patients treated with eliglustat were found to have an improvement in the primary endpoint of reduction in spleen volume at 9 months compared to placebo.
- Results of ENCORE reported eliglustat to be to be non-inferior to imiglucerase (an ERT) in the composite primary endpoint of stability in spleen volume, liver volume, Hgb level, and platelet count at 12 months compared to baseline.
- The quality of evidence for the use of eliglustat for the treatment of Gaucher disease type 1 is determined to be low (Refer to Appendix A).
- Available details of the Phase 3 clinical trials and results are included in the tables below.
- The trials were sponsored by Genzyme.

Trial	Inclusion	Duration	Treatment	Baseline
ENGAGE[1-4] R, DB, PC, MC	Gaucher disease type 1, splenomegaly, thrombocytopenia Treatment-naïve (allowed SRT > 6 months, ERT > 9 months prior to enrollment but 35 of 40 patients had no prior treatment)	9 months	Eliglustat (N=20) 42 mg twice daily, increased to 84 mg twice daily (85% of patients) depending on trough plasma concentrations Placebo (N=20)	ELG / PBO SV 13.89 / 12.5 Hgb 12.1 / 12.8 LV 1.44 / 1.36 Plt 75.05 / 78.48 Mean values 50% Male Age 16-63 yrs (mean 32)
ENCORE[1,2,4] R, OL, AC, MC	Gaucher disease type 1 Achieved therapeutic goals (SV < 10 x normal; Hgb ≥ 11 women, ≥ 12 men; LV < 1.5 x normal; Plt ≥ 100,000/mm^3; no bone crisis or sx bone disease past 1yr) with ERT (75% imiglucerase; 21% velaglucerase) ≥ 3 years	12 months	Eliglustat (N=99) 42 mg twice daily, increased to 84 and 127 mg twice daily at 4 week intervals depending on trough plasma concentrations Imiglucerase (N=47) Every 2 week regimen equivalent to ERT dose	ELG / IMG SV 3.2 / 2.6 Hgb 13.6 / 13.8 LV 0.9 / 0.9 Plt 207 / 192 ~45% Male Age 18-69 yrs (median 37.4)

AC=active-controlled; DB=double-blind; ELG=eliglustat; ERT=enzyme replacement therapy; Hgb=hemoglobin (g/dL); IMG=imiglucerase; LV=liver volume (in MN); MC=multi-center; MN=multiples of normal; OL=open-label; PBO=placebo; PC=placebo-controlled; Plt=platelet count (x 10^9/L); R=randomized; SRT= substrate reduction therapy; SV=spleen volume (in MN); sx=symptoms; yrs=years

ENGAGE and ENCORE Primary and Secondary Endpoint Results[1-3]

ENGAGE[2,3]	Eliglustat (N=20)	Placebo (N=20)	Difference (95% CI)	P
	Mean Change			
Spleen volume[a]	-27.77%	2.26%	-30.03 (-36.82, -23.24)	<0.001
Hgb (g/dL)	0.69	-0.54	1.22 (0.57, 1.88)	<0.001
Liver volume	-5.2%	1.4%	-6.64 (-11.37, -1.91)	0.007
Platelet count	32.0%	-9.1%	41.06 (23.95, 58.17)	<0.001
ENCORE[2]	**Eliglustat (N=99)**	**Imiglucerase (N=47)**	**(95% CI)**	
	Patients that Remained Stable[b]			
Composite[a,b]	84.8%	93.6%	(-17.6, 8.8)	Non-inferior[1,2,c]
Spleen volume[b]	95.8%	100%		
Hgb (g/dL)[b]	94.9%	100%		
Liver volume[b]	96.0%	93.6%		
Platelet count[b]	92.9%	100%		

[a]Primary endpoint
[b]Stability in spleen volume (< 25% increase), liver volume (< 20% increase), Hgb level (< 1.5 g/dL decrease), platelet count (< 25% decrease) from baseline to 12 months
[c]Pre-specified non-inferiority margin of -25% for primary efficacy endpoint was "deemed clinically unacceptable by the clinical review team"[3]

Safety

(for more detailed information refer to the product package insert)

	Comments
Contraindications[1]	• Patients who are CYP2D6 EM or IM that are taking a strong or moderate CYP2D6 inhibitor with a strong or moderate CYP3A inhibitor • Patients who are CYP2D6 IM or PM that are taking a strong CYP3A inhibitor
Warnings/Precautions[1]	• **ECG Changes and Potential for Cardiac Arrhythmias:** Not recommended in patients with pre-existing cardiac disease (congestive heart failure, recent acute myocardial infarction, bradycardia, heart block, ventricular arrhythmia), long QT syndrome, and concomitant use of Class 1A and Class III antiarrhythmics
Adverse Reactions[1]	
Common adverse reactions[1]	Fatigue, headache, nausea, diarrhea, back pain, pain in extremities, upper abdominal pain, reported in $\geq$ 10% of patients treated with eliglustat. Refer to product information for further details.

Drug Interactions[1]

Drug-Drug Interactions[1]

- Eliglustat is a CYP2D6 and CYP3A substrate and is metabolized primarily by the CYP2D6 isoenzyme. Concomitant use of eliglustat with medications that inhibit CYP2D6 and CYP3A may significantly increase eliglustat exposure with subsequent prolongation of the PR, QTc and/or QRS cardiac interval, with potential increased risk for arrhythmias.
- Systemic exposure of eliglustat is significantly decreased by strong CYP3A inducers; therefore, concomitant administration is not recommended in CYP2D6 EMs, IMs, or PMs.
- Eliglustat inhibits P-glycoprotein (P-gp) and CYP2D6; increased concentrations of medications that are P-gp or CYP2D6 subtrates may occur with concomitant administration of eliglustat. Dose reduction or monitoring is recommended as indicated.
- Refer to the tables below for recommendations based on potential drug interactions and/or metabolizer status.

Recommended Eliglustat Dosing Per Potential CYP450 Drug Interactions and CYP2D6 Metabolizer Status[1]

CYP450 Inhibitors		CYP2D6 EM Eliglustat Dose	CYP2D6 IM Eliglustat Dose
CYP2D6 Inhibitors in combination with CYP3A4 Inhibitors	Strong or Moderate in combination with Strong or Moderate	Eliglustat Contraindicated	
CYP2D6 Inhibitors	Strong (e.g., paroxetine)	84 mg once daily	84 mg once daily
CYP2D6 Inhibitors	Moderate (e.g., terbinafine)	84 mg once daily	84 mg once daily
CYP3A Inhibitors	Strong (e.g., ketoconazole)	84 mg once daily	Contraindicated
CYP3A Inhibitors	Moderate (e.g., fluconazole)	84 mg once daily	Not recommended

Recommended Eliglustat Dosing Per Potential CYP450 Drug Interactions in CYP2D6 Poor Metabolizers[1]

CYP450 Inhibitors		CYP2D6 PM Eliglustat Dose
CYP3A Inhibitors	Strong (e.g., ketoconazole)	Contraindicated
CYP3A Inhibitors	Moderate (e.g., fluconazole)	Not recommended
CYP3A Inhibitors	Weak (e.g., ranitidine)	Not recommended

Recommended Eliglustat Dosing Per Potential CYP450 Drug Interactions and CYP2D6 Metabolizer Status[1]

CYP450 Inducers		CYP2D6 EM, IM, PM Eliglustat Dose
CYP3A Inducers	Strong (e.g., rifampin, carbamazepine, phenobarbital, phenytoin, St. John's Wort)	Not recommended

Recommendations Based on Potential Drug Interactions with P-gp or CYP2D6 Substrates[1]

P-gp or CYP2D6 Substrates		Recommendations
P-gp Substrate	Digoxin	Measure serum digoxin level before starting eliglustat; decrease digoxin dose by 30%, with continued monitoring
Other P-gp Substrates	e.g., phenytoin, colchicine, dabigatran	Monitor drug concentrations, as indicated; or consider dose reduction of concomitant medication and titrate to clinical effect
CYP2D6 Substrates	Metoprolol; Tricyclic antidepressants (e.g., nortriptyline, amitriptyline, imipramine); Phenothiazines (e.g., perphenazine, chlorpromazine)	

Risk Evaluation

As of December 29, 2014

Comments

Sentinel event advisories

- None
- Sources: ISMP, FDA, TJC

Look-alike/sound-alike error potentials

NME Drug Name	Lexi-Comp	First DataBank	ISMP	Clinical Judgment
Eliglustat 84mg cap	None	None	None	Miglustat Alogliptin Eligard
Cerdelga	None	None	None	Cerezyme

- Sources: Based on clinical judgment and an evaluation of LASA information from three data sources (Lexi-Comp, First Databank, and ISMP Confused Drug Name List)

Dosing and Administration[1]

- Patients should have their CYP2D6 genotype determined by an FDA-cleared test to provide guidance on recommended dosing and potential for drug interactions. A specific dosage cannot be recommended for patients whose CYP2D6 genotype cannot be determined (indeterminate metabolizers).
- CYP2D6 EMs or IMs: **84 mg orally twice daily**
- CYP2D6 PMs: **84 mg orally once daily**
- Eliglustat capsules should be swallowed whole and not crushed, opened or dissolved.
- Patients taking eliglustat should avoid eating grapefruit or drinking grapefruit juice.

Special Populations (Adults)[1]

	Comments
Pregnancy	• Eliglustat is Pregnancy Category C • Only administer eliglustat if the potential benefit justifies the potential risk; may cause fetal harm based on animal data
Lactation	• Discontinue the drug or nursing based on the importance of the drug to the mother
Renal Impairment	• Not recommended in moderate to severe renal impairment
Hepatic Impairment	• Not recommended
Pharmacogenetics/genomics	• Eliglustat is a CYP2D6 and CYP3A substrate. The FDA label indication specifies patients with Gaucher disease type 1 who are CYP2D6 extensive metabolizers, intermediate metabolizers, or poor metabolizers as detected by an FDA-cleared test, as dosing and recommendations for potential drug interactions are based on the CYP2D6 metabolizer status. Information on FDA-cleared tests available at: http://www.fda.gov/medicaldevices/productsandmedicalprocedures/invitrodiagnostics/ucm330711.htm

Projected Place in Therapy

- Gaucher disease type 1 is an autosomal recessive disorder due to an insufficiency of the lysosomal enzyme glucocerebrosidase (also known as glucosylceramide synthase, or acid beta-glucosidase), leading to accumulation of the lipid glucocerebroside, or glucosylceramide, in the lysosome of macrophages, resulting in foam cells, also referred to as Gaucher cells. In Gaucher disease type 1, accumulation of these Gaucher cells occurs in the liver, spleen, bone marrow, as well as other organs including the lungs, resulting in hepatosplenomegaly, anemia, thrombocytopenia, pulmonary disease, and bone abnormalities including fractures and arthritis. Type 1 is the most common form of Gaucher disease and may manifest itself during childhood (with nearly half diagnosed by age 10) or anytime up through adulthood. Gaucher disease types 2 and 3 are characterized by affecting the central nervous system. The prevalence of Gaucher disease is estimated to be 1 in 57,000 live births, with type 1 having a higher prevalence in people of Ashkenazi (eastern and central European) Jewish descent. It is estimated that there are approximately 12,000 people in the United States with Gaucher disease type 1.[9-13]
- Current pharmacologic treatment for Gaucher disease type 1 includes substrate reduction therapy (SRT) or enzyme replacement therapy (ERT). The available enzyme replacement therapies include: imiglucerase, an analogue of glucocerebrosidase produced by recombinant DNA technology using Chinese hamster ovary cells;[6] taliglucerase alfa, a hydrolytic lysosomal glucocerebroside-specific enzyme (active form of the enzyme beta-glucocerebrosidase produced by recombinant DNA technology using carrot plant cell culture);[7] and velaglucerase alfa, a glycoprotein formed by gene activation in human fibroblasts, which has the same amino acid sequence as glucocerebrosidase.[8] The three ERTs are available in vials for reconstitution and are administered by intravenous infusion. The two substrate reduction therapies are available as oral formulations and include: miglustat, a glucosylceramide synthase inhibitor indicated as monotherapy for the treatment of mild to moderate Gaucher disease type 1 in patients where ERT is not an option (e.g., due to allergy, hypersensitivity, or poor venous access);[5] and eliglustat, a glucosylceramide analogue, and inhibitor of glucosylceramide synthase, approved for the long-term treatment of adult patients with Gaucher disease type 1 who are CYP2D6 extensive metabolizers, intermediate metabolizers, or poor metabolizers as detected by an FDA-cleared test.[1]

- As with other therapeutic proteins, the development of anti-drug antibodies has occurred with use of the ERTs. Hypersensitivity reactions have been reported with the ERTs and should be managed according to the severity of the reaction, with decreasing or temporarily stopping the infusion, or use of antihistamines, antipyretics, and/or corticosteroids. Anaphylaxis reactions have also been reported and should be managed by immediate discontinuation of the infusion and initiation of appropriate medical treatment.[6-8,13] Additional considerations for treatment with ERT include intravenous infusion time (and travel and/or personnel time, as indicated). Precautions with the use of miglustat include diarrhea (occurring in up to 85% of patients) and weight loss, peripheral neuropathy, tremor, and reductions in platelet count; it is recommended that therapy with miglustat be directed by providers knowledgeable about the treatment of Gaucher disease.[5]
- Enzyme replacement therapy has been the standard of care for Gaucher disease type 1 and is effective for improving the associated hematologic and visceral abnormalities, and bone disease.[12] The SRT miglustat, is recommended in patients with Gaucher type 1 where ERT is not an option; miglustat was not as effective as an ERT in a comparison trial and has significant side effects.[5,14] The optimal place in therapy of eliglustat in Gaucher disease type 1 has not been established. Eliglustat was effective compared to placebo in treatment-naïve patients and non-inferior to the ERT imiglucerase, in treatment-experienced patients; however, the long-term outcome benefit and treatment effect on associated bone disease has yet to be established.
- Treatment considerations should take into account the risk vs. benefit of available therapies, including patient considerations such as treatment response, safety concerns, adverse effects and tolerability, route of administration, as well as the cost of and access to therapy. Due to the potential for drug interactions with eliglustat, and other safety and efficacy considerations based on the patient's CYP2D6 metabolizer status, patients should have genetic testing by an FDA-cleared test to determine whether they are CYP2D6 extensive metabolizers, intermediate metabolizers, or poor metabolizers, for appropriate dosing and to allow for considerations for potential drug interactions:
    - Serious adverse events with eliglustat include ECG changes and potential for cardiac arrhythmias; eliglustat is not recommended in patients with pre-existing cardiac disease, long QT syndrome, and concomitant use of Class 1A and Class III antiarrhythmics.
    - Eliglustat is a CYP2D6 and CYP3A substrate and is metabolized primarily by the CYP2D6 isoenzyme. Concomitant use of eliglustat with medications that inhibit CYP2D6 and CYP3A may significantly increase eliglustat exposure with subsequent prolongation of the PR, QTc and/or QRS cardiac interval, with potential increased risk for arrhythmias.
    - Eliglustat is contraindicated in patients who are CYP2D6 extensive metabolizers or intermediate metabolizers that are taking a strong or moderate CYP2D6 inhibitor with a strong or moderate CYP3A inhibitor and in patients who are CYP2D6 intermediate metabolizers or poor metabolizers that are taking a strong CYP3A inhibitor.
    - Refer to the Safety section of this monograph or the product package insert for additional recommendations and considerations for potential drug interactions.
- It would be expected that the prevalence of Gaucher disease type 1 in the Veteran population would be very low. Under these circumstances, it would be anticipated that utilization of treatments for this condition would be minimal.
- The quality of evidence for the use of eliglustat for the treatment of Gaucher disease type 1 is determined to be low (Refer to Appendix A).

References

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Appendix A: GRADEing the Evidence

Designations of Quality

Quality of evidence designation	Description
High	Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes (2 consistent, higher-quality randomized controlled trials or multiple, consistent observational studies with no significant methodological flaws showing large effects).
Moderate	Evidence is sufficient to determine effects on health outcomes, but the number, quality, size, or consistency of included studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes (1 higher-quality trial with > 100 participants; 2 higher-quality trials with some inconsistency; 2 consistent, lower-quality trials; or multiple, consistent observational studies with no significant methodological flaws showing at least moderate effects) limits the strength of the evidence.
Low	Evidence is insufficient to assess effects on health outcomes because of limited number or power of studies, large and unexplained inconsistency between higher-quality studies, important flaws in study design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.

Please refer to Qaseem A, et al. The development of clinical practice guidelines and guidance statements of the American College of Physicians: Summary of Methods. Ann Intern Med 2010;153:194-199.